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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,913	10/10/2001	Ashley I. Bush	0609.4540003	5681

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EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,913	BUSH ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-46* is/are pending in the application.

4a) Of the above claim(s) *7,9,10,19,27,28,36 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-6, 8, 11-18, 20-26, 29-35, 37-43, 45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Information Disclosure Statement (IDS) filed 07/27/04, the Response under 37 CFR §1.111, Applicants' Arguments/Remarks and the petition for extension of time (2 months-granted) under 37 CFR 1.136(a)(1), all filed 05/17/04 is acknowledged.

Applicant's election with traverse of *oral* administration form and formulations administered *sequentially* in the reply filed on 05/17/04 is acknowledged. The traversal is on the ground(s) that 'the methods and compositions encompassed by the present claims are closely related to one another regardless of the manner of administration (orally, intramuscularly, parenterally or intradermally), or the administration regimen used (sequential or simultaneous administration)'. This is not found persuasive because a separate search would be necessary for each form of administration (oral, intramuscular, parenteral, intradermal) and for each administration regimen (simultaneous or sequential), thereby creating a burdensome search. Additionally, the distinct forms of administration and administration regimens are not recognized as being equivalent in the art. Therefore, the issue of patentability must be determined individually.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7, 9, 10, 19, 27, 28, 36 & 44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 05/17/04.

Claims 1, 3-6, 8, 11-18, 20-26, 29-35, 37-43, 45 and 46 are pending. Claim 2 has been cancelled. Claims 1, 3-6, 8, 11-18, 20-26, 29-35, 37-43, 45 and 46 are rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-6, 8, 11-18, 20-26, 29-33, 37-41, 45 and 46 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Gerolymatos (US Pat. No. 6,001,852).

Gerolymatos discloses a pharmaceutical composition and methods for the treatment and prevention of Alzheimer's disease (AD) comprising clioquinol alone or clioquinol in combination with Vitamin B_{12} and optionally, pharmaceutically acceptable carriers and/or excipients. The use of the pharmaceutical composition removes or alleviates the side effects of clioquinol (see Abstract & Claims) and (column 4, lines 26-34).

Clioquinol may be administered in any appropriate amount in any suitable galenic formulation and following any regime of administration (col. 6, lines 63-65). According to

Gerolymatos, clioquinol is believed to have the ability to penetrate the blood-brain barrier, to effectively chelate heavy metals to prevent the aggregation of amyloid, and to redissolve amyloid deposit (col. 6, lines 43-49).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-6, 8, 11-18, 20-26, 29-35, 37-43, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerolymatos (US Pat. No. 6,001,852).

Gerolymatos, as delineated above, teaches a pharmaceutical composition and methods for the treatment and prevention of Alzheimer's disease (AD) comprising clioquinol alone or clioquinol in combination with Vitamin B_{12} and optionally, pharmaceutically acceptable carriers

and/or excipients. The use of the pharmaceutical composition removes or alleviates the side effects of clioquinol (see Abstract & Claims) and (column 4, lines 26-34).

Clioquinol may be administered in any appropriate amount in any suitable galenic formulation and following any regime of administration (col. 6, line 63 – col. 7, line 12). According to Gerolymatos, clioquinol is believed to have the ability to penetrate the blood-brain barrier, to effectively chelate heavy metals to prevent the aggregation of amyloid, and to redissolve amyloid deposit (col. 6, lines 43-49).

Therapeutic formulations include those suitable for parenteral, oral, rectal or intradermal administration, of which, oral administration is the preferred route (col. 8, lines 42-50). The clioquinol and/or Vitamin B_{12} in the pharmaceutical composition are purified and are of high purity (col. 8, lines 5-30).

A therapeutically effective amount of clioquinol taught is 5 to 250 mg (instant range is 5-10 mg/kg). A suitable amount of Vitamin B_{12}, effective to inhibit clioquinol-related side effects is, 5 μg to 2 mg and 0.5 to 1 mg (instant range is 7-10 mg/kg and 70-100 μg/kg) (see col. 8, lines 30-38).

Clioquinol and Vitamin B_{12} can be administered concurrently, concurrently but separately or sequentially (col. 8, lines 38-41). If clioquinol and Vitamin B_{12} are administered sequentially, the entity comprising clioquinol is preferably administered for one to three weeks followed by a wash-out period of one to four weeks during which the entity comprising Vitamin B_{12} is administered, but the entity comprising clioquinol is not administered. After the wash-out period, the treatment can be repeated (col. 10, lines 15-27).

Gerolymatos teaches that for the prevention of the onset of the symptoms and signs of Alzheimer's disease, or for the delay of the symptoms and signs in the evolution of the disease, daily clioquinol dosages of up to 100 mg or less can be administered for long periods, viz. up to ten years (col. 7, lines 13-17). If clioquinol is administered for prolonged periods, it is preferably administered intermittently. In a first period, clioquinol may be administered, e.g., for one to three weeks followed by a wash-out period, which may be one to four weeks. After the wash-out period, the first period may be repeated. If Vitamin B_{12} is administered, such administration may take place during the clioquinol administration period, during the wash-out period, or during both periods. The long-term intermittent therapy provides for the resolubilisation and the prophylactic inhibition of zinc-Aß aggregates. The intermittent administration of clioquinol also reduces the toxicity potential of the drug so that treatment may be extended throughout the evolution of the disease (col. 7, lines 13-64).

The examples at columns 10-14 demonstrate pharmaceutical formulations and studies based on clioquinol and Vitamin B_{12}.

Gerolymatos teaches a suitable amount of Vitamin B12 of 5 µg to 2 mg and 0.5 to 1 mg, to effectively inhibit clioquinol-related side effects (col. 8, lines 33-36) and also teaches that actually administered amounts may be decided by a supervising physician. Gerolymatos is deficient only in the sense that he does not teach the instant amount range of Vitamin B_{12}.

However, it is deemed obvious to one of ordinary skill in the art to determine suitable amounts of any ingredient, particularly vitamins, through the use of routine or manipulative experimentation to obtain the best possible results, based on the intended or desired purpose, as these are indeed variable parameters. Moreover, generally differences in concentration will not

support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case, no criticality is observed in the instant Vitamin B_{12} range, since the prior art clearly teaches compositions and methods for the prevention or treatment of Alzheimer's disease utilizing therapeutically effective amounts of clioquinol, Vitamin B_{12} and pharmaceutically acceptable carriers and excipients. Thus, the instant invention is rendered *prima facie* obvious over the prior art of record.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

US Patent No. 5,994,323 Gerolymatos (11/1999)

WO 98/06403 Gerolymatos (02/1998)

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays from 8:00 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

H. N. Sheikh H.N.S.

Patent Examiner

Art Unit 1615

September 27, 2004

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600